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Cyclopropene Derivatives as Precursors to Enantioenriched Cyclopropanols and *n*-Butenals Possessing Quaternary Carbon Stereocenters**

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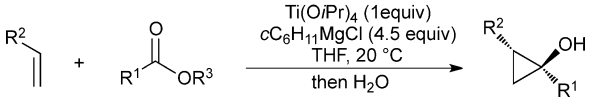
Dedicated to Professor Peter Vollhardt on the occasion of his 69th birthday

Abstract: *The diastereoselective carbocupration reaction of cyclopropenylmethyl ethers followed by addition of oxenoid leads to the formation of diastereo- and enantiomerically enriched 2,2,3,3-tetrasubstituted cyclopropanol derivatives. Ring fragmentation of the copper cyclopropanolate leads to acyclic butenal derivatives possessing enantiomerically enriched α-quaternary carbon stereocenters in a single-pot operation.*

Since the pioneering report of Perkin,[1] the field of small-ring chemistry, and particularly three-membered rings, has been extensively investigated and reviewed over the years.[2] Among all the possible three-membered ring subunits that have been reported, cyclopropanol derivatives have recently attracted a lot of attention as they are found in many natural products and they may undergo, in addition, a large variety of synthetic transformations.[3] Various strategies can provide cyclopropanols[4] but the most efficient and powerful approach is certainly the Kulinkovich reaction which transforms esters into cyclopropanols by the addition of Grignard reagents to titanium isopropoxide.[5] As the first intermediate of the Kulinkovich transformation is the formation of a titanacyclopropane derivative,[6] the latter can also be generated in situ by addition of Grignard reagents to an alkene in the presence of $Ti(OiPr)_4$ (Scheme 1).[6,7] For the reaction to proceed, it is essential that the carbon–carbon double bond of the alkene be only monosubstituted, thus resulting in the predominant formation of (*E*)-1,2-disubstituted cyclopropanol.[6,7] Moreover, the enantioselective formation of cyclopropanols could be achieved with ethyl acetate in good enantiomeric ratios with titanium spiro-TADDOLate,[8] or with hexafluoroisopropyl alkanoates.[9]

Kulinkovich reaction



Scheme 1. General scheme for the Kulinkovich reaction. THF = tetrahydrofuran.

However, despite all of these achievements, the preparation of 2,2,3,3-polysubstituted cyclopropanols in a diastereo- and enantiomerically enriched form, particularly with two adjacent all-carbon quaternary stereocenters, cannot be achieved by the Kulinkovich reaction and is therefore in its complete infancy. Because of the importance of cyclopropanols in synthesis, new and efficient approaches are needed to solve this challenging problem. In addition, if the strategy leading to the preparation of polysubstituted cyclopropanols could also be used to prepare quaternary carbon stereocenters in acyclic systems, by selective ring opening of the three-membered ring, it would certainly be a very useful tool for the preparation of important building blocks in organic synthesis. It should be noted that the impediment to synthesis presented by the formation of quaternary carbon stereocenter arises from the steric congestion imposed by the four attached carbon atoms and by the number of degrees of freedom associated with these structures when acyclic systems are concerned.[10] In this context, we[11] and others[12] have been interested in this problem and have reported several approaches leading to the desired quaternary stereocenter in acyclic systems with the creation of several carbon–carbon bonds per chemical step. Herein, we disclose a protocol for the direct preparation of diastereoisomerically pure and enantiomerically enriched 2,2,3,3-polysubstituted cyclopropanols, and by subsequent selective fragmentation into enantiomerically enriched acyclic butenal derivatives possessing the desired α-quaternary carbon stereocenter (Scheme 2). Our general strategy is based on the diastereoselective carbometalation reaction of easily accessible cyclopropenyl derivatives (**1**),[13] and subsequent oxidation reaction of the resulting cyclopropyl metal species **2** into metal cyclopropanolate **3**. After acidic hydrolysis, the cyclopropanol **4** possessing two adjacent quaternary carbon stereocenters should be obtained, whereas a selective ring fragmentation

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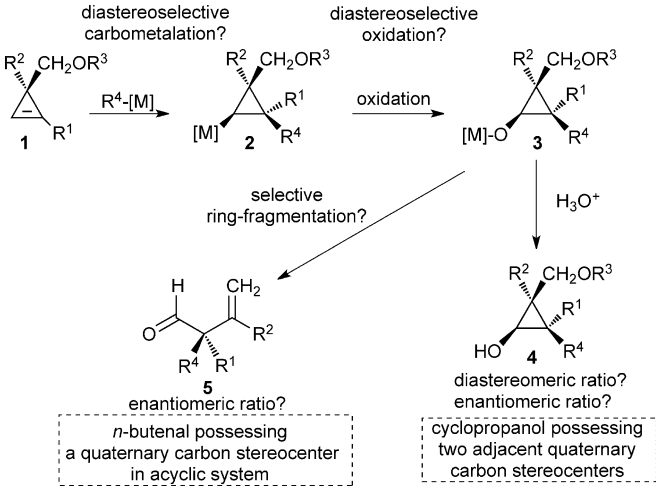
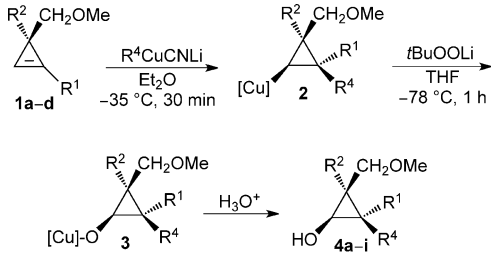


Scheme 2. Proposed access to 2,2,3,3-polysubstituted cyclopropanol and *n*-butenal possessing quaternary carbon stereocenters.

would give access to acyclic butenal possessing the all-carbon quaternary stereocenter (**5**). Notably, the stereogenic center in the initial cyclopropenyl derivatives **1** will induce the diastereoselectivity during the carbometalation step (diastereoselective formation of **2**). However, this initial stereogenic center will then be lost during the ring fragmentation and the diastereoselectivity of the carbometalation reaction of cyclopropenes (in **2**) will be therefore transferred into the enantioselectivity of the end product **5**.

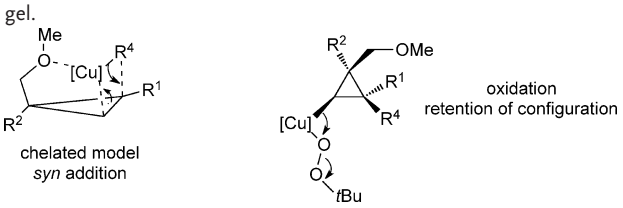
We initially focused our attention on the diastereoselective preparation of the polysubstituted cyclopropanol **4** and we were pleased to observe that the first step of the sequence, namely the carbocupration of **1a–d** (Table 1), proceeds rapidly under mild reaction conditions with $R^4CuCNLi$ (−35 °C, 30 min) in Et_2O.[14] The expected cyclopropyl copper species **2** was obtained in good yields and excellent diastereoselectivity (d.r. > 98:2) after hydrolysis. The configuration of the major isomer was determined by chemical correlation, thus confirming the *syn* diastereoselectivity of the carbocupration reaction.[15] This stereoselectivity can be rationalized by the existence of a chelated transition state between the Lewis base of the ether and the organometallic species (see footnotes of Table 1). Having in hand the cyclopropylcopper species, a selective oxidation reaction needs to be performed with complete retention of configuration. In contrast to the oxidation with O_2 where a rapid degradation of the cyclopropylcopper is observed (oxidative dimerization),[16] the oxidation with ambiphilic lithiated hydroperoxide or oxenoid (*t*BuOOLi),[17] simply generated by deprotonation of *t*BuOOH with *n*BuLi, led to the copper alkoxide without the formation of free radical intermediates (see footnotes of Table 1). After acidic hydrolysis, the corresponding 2,2,3,3-tetrasubstituted cyclopropanols **4a–i** were obtained as single diastereoisomers (entries 1–9). The reaction proceeds similarly when R^1 is a primary or secondary alkyl group (compare entries 1–7 with 8 and 9), when R^2 is an alkyl or aryl group (compare entries 1–5 and 6 and 7), and when R^4 is an alkyl or aryl group (compare all entries with entry 4). It is interesting to note that although phenyl and methyl copper species are known to generally react very

Table 1: Diastereoselective formation of the 2,2,3,3-tetrasubstituted cyclopropanols **4a–i**.



Entry	R^1	R^2	R^4	d.r.[a]	Yield [%][b]
1	Pr	Ph (**1a**)	Me	99:1:0:0	70 (**4a**)
2	Pr	Ph (**1a**)	Bu	99:1:0:0	90 (**4b**)
3	Pr	Ph (**1a**)	Hex	99:1:0:0	66 (**4c**)
4	Pr	Ph (**1a**)	Ph	99:1:0:0	72 (**4d**)
5	Bu	Ph (**1b**)	Me	99:1:0:0	68 (**4e**)
6	Hex	Me (**1c**)	Me	99:1:0:0	69 (**4f**)
7	Hex	Me (**1c**)	Bu	99:1:0:0	63 (**4g**)
8	*c*Hex	Ph (**1d**)	Bu	99:1:0:0	67 (**4h**)
9	*c*Hex	Ph (**1d**)	Me	99:1:0:0	65 (**4i**)

[a] Determined by ^1H NMR analysis of the crude reaction mixture. [b] Determined after purification by column chromatography on silica gel.

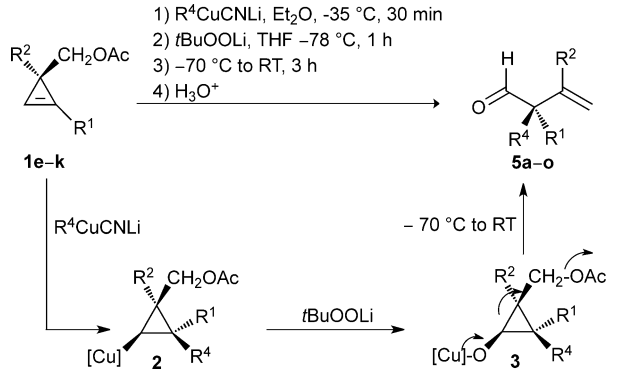


sluggishly in carbocupration reaction, the strain released by the carbocupration of the cyclopropenylmethyl ethers **1a–d** allows the reaction to proceed quickly and in good yields. The stereochemistry of the secondary alcohol was determined by nuclear overhauser experiments (see the Supporting Information) and proceed with pure retention of configuration at the metalated center, thus suggesting that the oxidation reaction presumably proceeds through an intramolecular S_N2 reaction (1,2-metalate rearrangement).[18]

As we have a direct approach to the polysubstituted copper cyclopropanolate **3** as a single diastereoisomer and in a single-pot operation from the cyclopropenyl ether **1**, we were then interested in using the inherent ring strain of these three-membered rings to perform the subsequent selective carbon–carbon bond fragmentation as a new entry to the acyclic enal **5**, which possesses the desired quaternary carbon stereocenter (Scheme 2).[19] However, when **3e** (R^1 = Bu, R^2 = Ph, R^3 = Me) was warmed to room temperature or even refluxed for few hours in THF, the ring fragmentation was not observed and the cyclopropanol **4e** was quantitatively recovered after hydrolysis. Similarly, addition of a Lewis acid such as $BF_3{\cdot}OEt_2$ to **3e** did not promote the fragmentation.

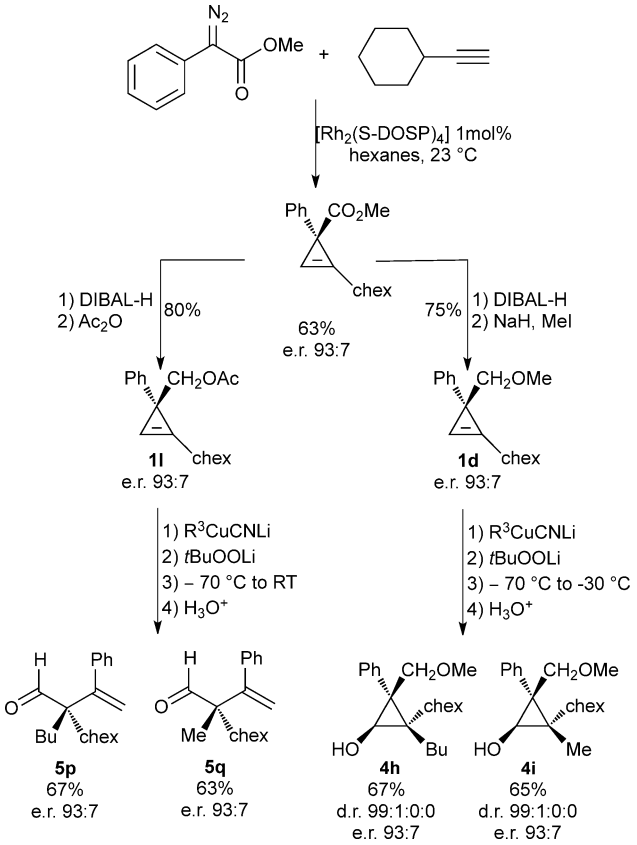
So it was clear that for the carbon–carbon bond fragmentation to occur, a better leaving group was needed.[20] As it was equally important that the whole sequence of carbometalation/oxidation be completely diastereoselective, we decided to investigate the case of structurally related cyclopropenyl methyl derivatives and we focused on the cyclo-

Table 2: One-pot formation of the *n*-butenal **4** possessing a quaternary carbon stereocenter.



Entry	R^1	R^2	R^4	Yield [%][a]
1	Pr	Ph (**1e**)	Me	74 (**5a**)
2	Pr	Ph (**1e**)	Bu	66 (**5b**)
3	Pr	Ph (**1e**)	Hex	64 (**5c**)
4	Pr	Ph (**1e**)	Ph	68 (**5d**)
5	Hex	Ph (**1f**)	Me	74 (**5e**)
6	Hex	Ph (**1f**)	Bu	66 (**5f**)
7	Hex	Ph (**1f**)	Ph	65 (**5g**)
8	Tol	Ph (**1g**)	Me	67 (**5h**)
9	Tol	Ph (**1g**)	Bu	60 (**5i**)
10	Bu	Ph (**1h**)	Ph	68 (**5j**)
11	1-cyclohexenyl	Ph (**1i**)	Me	60 (**5k**)
12	$PhCH_2O(CH_2)_2$	Ph (**1j**)	Bu	70 (**5l**)
13	$PhCH_2O(CH_2)_2$	Ph (**1j**)	Ph	70 (**5m**)
14	Hex	Me (**1k**)	Me	60 (**5n**)
15	Hex	Me (**1k**)	Ph	62 (**5o**)

[a] Determined after purification by column chromatography on silica gel.



Scheme 3. One-pot preparation of enantiomerically enriched cyclopropanol (**4**) and butenal (**5**) derivatives. DIBAL-H = diisobutylaluminum hydride.

propenylmethyl esters **1e–k** (Table 2). The carbocupration reaction proceeds, here again, smoothly for a large variety of diversely substituted cyclopropenylmethyl esters (**1e–k**; R^1 = alkyl, aryl, cyclohexenyl), with various organocuprate reagents (R^4 = alkyl, aryl) and as before, R^2 could be an aryl or an alkyl group. In all cases, the carbocupration reaction is completely *syn* diastereoselective, as determined after hydrolysis and chemical correlations.[13] The subsequent oxidation reaction is performed at low temperature and the corresponding copper cyclopropanolate **3**, by slowly warming the reaction mixture from −78 to 0 °C over 3 hours, is transformed into the expected *n*-butenal **5** through a selective ring fragmentation reaction.[21] *n*-Butenal possessing the all-carbon quaternary stereocenter could therefore be easily prepared in a single-pot operation and in good yields from the easily accessible cyclopropenyl esters **1e–k** as described in Table 2. It should be noted that this single-pot strategy allows the formation of various combinations of quaternary carbon stereocenters in acyclic systems (with alkyl, vinyl, phenyl groups).[22] Having established an easy protocol for the preparation of either **4** or **5** from simple starting materials, the enantioselective synthesis of the cyclopropenylmethyl ether **1d** and cyclopropenylmethyl ester **1l** were easily achieved in high enantiomeric ratio (e.r. 93:7) through cyclopropenation of the terminal alkyne with methyl phenyldiazoacetate and $[Rh_2(S\text{-DOSP})_4]$ as the catalyst (Scheme 3).[23]

The combined diastereoselective carbometalation reaction followed by selective oxidation of **1d** proceeds to give the enantiomerically enriched cyclopropanols **4h,i** as a single diastereoisomer with the same enantiomeric ratio as the starting material (Scheme 3, d.r. > 99:1:0:0; e.r. 93:7; see the Supporting Information). Using the same combined strategy on **1l**, the *n*-butenal derivatives **5p,q** were obtained in a single-pot operation with a high enantiomeric ratio (e.r. 93:7) and good yields upon isolation (Scheme 3; see the Supporting Information). Therefore, a complete transfer of chirality is observed in this tandem reaction.

In conclusion, the *syn*-diastereoselective carbometalation of cyclopropenyl esters and ethers lead to the corresponding cyclopropyl copper derivatives in excellent yields and diastereoselectivity. A subsequent oxidation reaction, easily performed by addition of oxenoid to the reaction mixture, gives either the diastereoisomerically pure 2,2,3,3-polysubstituted cyclopropanol derivatives **4** or *n*-butenal species **5** possessing the challenging quaternary carbon stereocenter in acyclic systems through a fragmentation reaction. All of these transformations are performed in a single-pot operation and provide an easy and unique access to otherwise difficult molecules.

Keywords: copper · metalation · small-ring systems · strained molecules · synthetic methods

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